Original Articles

CLINICAL PROFILE AND RISK FACTORS FOR ORAL CANDIDOSIS IN SICK NEWBORNS

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ABSTRACT

Objectives: *To provide the clinical profile and assess the significance of various risk factors contributing to the occurrence of oral candidosis in newborns.* ***Design:*** *Case-control study.* ***Setting:*** *Neonatal Intensive Care Unit (NICU).* ***Subjects:*** *Twenty newborns with oral candidosis and an equal number of age and weight matched controls.* ***Interventions:*** *All cases of oral candidosis were treated zvith local application of 1% Clotrimazole.* ***Results:*** *Oral candidosis was documented in 3.2% (20/650) cases in the NICU. Acute pseudomembranous candidosis was the most common presentation. The mean age of onset was 10.5 days. Candida albicans was isolated in 50% cases in addition to C. tropicalis, C. paratropicalis,* C. *krusei, C. glabrata and C. parapsilosis. On univariate analysis, male sex, birth asphyxia and prolonged antibiotic therapy had a significant correlation with occurrence of oral candidosis in neonates. Out of these, birth asphyxia was the only factor significantly associated with oral candidosis (OR 8.09, 95% CI 1.34-48.8, p=0.0226) on multivariate analysis.* ***Conclusions:*** *C. albicans was the predominant isolate in this series of oral candidosis. Clinical manifestations were evident in the second week of life and birth asphyxia was the most important associated perinatal event.*

Key words: *Oral Candidosis, Neonate.*

CANDIDA, a harmless commensal of digestive and vaginal tracts may occasionally cause disease(l). The spectrum of diseases caused by Candida in neonates extends from thrush and diaper rash to life-threatening septicemia and meningitis(2). Oral thrush in neonates is conventionally described as moniliasis or candidiasis. According to modern taxonomy however, moniliasis is now reserved for fungal infections in plants while candidosis is the accepted term for human infections(3).

Candidosis is the most common mycotic infection of the oral cavity of newborns(4). Though the neonatal age group is recognized as a potential risk factor for the development of oral thrush(5), not all babies who harbor Candida in their oral cavities progress to clinical disease(6-9). The evaluation and relative contribution of various factors leading to oral candidosis in neonates needs a systemic study. The present study was, therefore, conducted to identify those clinical attributes that make neonates susceptible to oral candidosis.

Subjects and Methods

Infants admitted to University College of Medical Sciences and G.T.B. Hospital Neonatal Intensive Care Unit (NICU) from February to September 1992 were screened for oral candidosis based on the diagnostic

criteria suggested by Rogers(l0). These included: *(i)* presence of clinical changes consistent with oral candidosis; *(ii)* presence of a large number of Candida like hyphae or pseudohyphae in smears taken from the lesion; and *(iii)* heavy yield of *Candida* species in culture from the lesion.

One control infant was identified for each case of candidosis. The criteria for selection included: *(i)* admission to the NICU within 24 h of the index case; (*ii)* gestational age within 1 week of the index case; and *(iii)* birth weight within 10% of the birth weight of the index case.

The data collected included obstetric risk factors, duration of labor, birth asphyxia, nursing care, birth weight, gestational age, day of onset and clinical course during the hospital stay. Treatment details regarding days of exposure to intravenous catheters, antibiotics, fat emulsions, ventilation and oxygenation were included. A feeding chart indicating the route of feeding and type of milk used was maintained. None of the babies in the study or control groups received steroids. The study cases were treated with local application of clotrimazole 1% solution applied thrice daily for seven days. After discharge, these cases were followed up for a duration of three months.

The study and control groups were matched for birth weight, gestational age and postnatal age. Mean birth weight and gestational age of study group was 1722.5 ± 577.7 g (median 1600 g; range 900 to 3200 g) and 34.4 ±4.1 weeks (median 34 weeks; range 28 to 40 weeks), respectively. For the controls, the mean birth weight and gestational age were 1600 + 514.8 g (median 1500 g; range, 1000-2900 g) arid 34.5 ± 3.5 weeks (median 34.5; range 28 to 40 weeks). These two groups, comprising of 20 new-borns each, were compared with respect to their exposure to various epidemiological and clinical risk factors. Statistical analysis was done using the SPSS software on compatible IBM PC/AT 386 computer. Chi-square, Student's 't' test and Fischer's exact tests were used for Univariate analysis. Factors found to be significant in the univariate analysis were further included in a multiple logistic regression model to identify their independent relationship.

Results

Among 650 children admitted to the NICU during the study period, twenty cases (3.2%) of oral candidosis were documented. Acute pseudomembranous candidosis was the most common variety observed in 19 infants. It was characterized by white creamy patches, fleks, coat or fur which on scraping, left an erythematous mucosal surface. One neonate had erythematous candidosis (loss of papillae on tongue with erythema). The mean age at onset of oral candidosis was 10.4 ± 2.9 days (median 9.5 days; range 7 to 18 days). Clinical symptoms apart from presence of white specks or fur, were noticed in only 5 neonates. Refusal to feed was the main complaint in 3 babies while 2 neonates showed poor weight gain.

Candida albicans was the most common causative organism isolated in 50% cases. The other species included C. *tropicalis* (15%), C. *paratropicalis* (10%), C. *krusei* (10%), C. *glabrata* (10%) and C. *pampsilosis* in 5% cases. After application of clotrimazole solution, lesions disappeared completely within four days of starting therapy (median 4 days; range 2 to 6 days) in all cases. Twelve cases could be followed up for duration of three months and none of them developed recurrence of oral thrush.

Risk factors for oral candidosis are

presented in *Table I.* Male sex and birth asphyxia were the only significant risk factors on univariate analysis. It was also observed that neonates developing candidosis received antibiotics for a significantly longer duration (6.05 ± 3.7 days) as compared to the control group (3.5 ± 3.5 days) ($p < 0.05$)

Multiple logistic regression analysis was subsequently performed. The model included two dichotomous (sex and birth asphyxia) and one continuous variable (duration of antibiotic therapy). Birth asphyxia was the only significant factor responsible for the occurence of oral candidosis in neonates (odds ratio 8.09; 95% confidence interval 1.34-48.8; p=0.0226).

TABLE I—*Risk Factors in Relation to Oral Candidosis*

Parameter	Study (n=20)	Control (n=20)
Sex		
Male*	16 (80)	8 (40)
Female	4 (20)	12 (60)
Birth place		
Inborn	11 (55)	13 (65)
Outborn	9 (45)	7 (35)
Delivery		
Vaginal	16 (80)	16 (80)
Cesarean	4 (20)	4 (20)
Obstetrical risk factors		
Present	9 (45)	11 (55)
Absent	11 (55)	9 (45)
Apgar score <5 at 1 min*	11 (55)	2 (10)
Infants not fed enterally	1 (5)	3 (15)
Route of feeding		
Breast	3 (15)	4 (20)
Bottle	3 (15)	1 (5)
Gavage	7 (35)	8 (40)
Mixed	6 (30)	4 (20)
Type of milk		
Breast	9 (45)	7 (35)
Formula	8 (40)	6 (30)
Mixed	2 (10)	4 (20)
Treatment		
Intravenous fluid	19 (95)	15 (75)
Antibiotics	17 (85)	11 (55)
Intravenous lipids	6 (30)	4 (20)
Ventilation	2 (10)	2 (10)
Oxygen administration	14 (70)	10 (50)

* $p < 0.05$
Figures in parenthesis indicate percentages.

Discussion

With the advent of potent antibacterial drugs and increased survival of immuno-compromised patients, fungi have become important pathogens. *Candida* species are the most common, usually beginning as an infection of the oral cavity. In adults it is unusual to have oral candidosis unless the host is compromised. Oral candidosis in neonates is documented in 0.5 to 20% of subjects in different studies(ll-15). At our NICU, the corresponding figure was 3% of all admissions.

Acute pseudomembranous candidosis is the most common presentation in neonates. However, in the present report, one newborn was also noticed to have erythematous and atrophic candidosis; as a consequence of the mother scraping the fur off the tongue. Oral candidosis typically arises after first week of life with maximum cases occuring between 7-10 days(14,16). In the present study, most of the infants were affected on the 10th day of their life. The mean age of colonization was not studied. Oral candidosis may occur in the form of pulpitis, gingivitis, tonsillitis, cheilitis, glossitis, stomatitis, pharyngitis, laryngitis, sinusitis and esophagitis(11). Though we did not

examine the larynx and esophagus routinely, the absence of dysphagia, hoarse cry and aspiration excluded their involvement. Most of our cases were asymptomatic (75%). One neonate having atrophic candidosis was diagnosed only after he refused to suck, probably due to soreness of tongue.

According to the western literature, the most frequent etiological agent for oral candidosis in neonates is *Candida albicans*(7,11,17). A preponderance of C. *albicans* isolates (50%) was also noticed in this study. Two earlier Indian studies, however, have documented higher isolation rates of C. *tropicallis, C. pseudotropicalis* and C. *stellatoidea* from oral specimens(8,9). Controversy still exists regarding the best drug to treat oropharyngeal candidosis. Gentian violet, nystatin and miconazole have been used in the past(l). We used clotrimazole, a safe and effective imidazole derivative, in our patients for a duration of one week and recurrence was not noticed in any of the cases, who were followed up for three months.

Multiple local and systemic factors predispose to *Candida* infections(5). Various workers have held the following host factors responsible for the newborn's susceptibility to oral candidosis: *(i)* immaturity of the immune system; *(ii)* lack of a mature oral microflora; *(iii)* prematurity; *(iv)* steroid and antibiotic therapy; and *(v)* local trauma(8). Prematurity and low birth weight (LBW) do not seem, however, to have any direct link with occurence of oral candidosis, as reported earlier(14,16,18). Infants born of Cesarean sections are equally prone to develop oral candidosis as products of vaginal delivery(9,16). A male preponderance in our patients was observed confirming the findings of Anderson(14) but contrary to others(9,16).

An Apgar score <5 was significantly associated with increased risk of oral candidosis on both univariate and multivariate analysis. All neonates having asphyxia received some form of resuscitation which could have resulted in local trauma and disintegration of oral mucosa. Disrupted mucosal barrier promotes adhesion of yeasts to the underlying epithelium(5). At the same time birth asphyxia may interfere with normal salivary flow which is integral to the maintenance of normal microflora in mouth. Disturbed microflora and mucosal breaks provide opportunities for fungal growth in the oral cavity.

Kaul(8) found an increased incidence of thrush in artificially fed babies. Our results are similar to those of Shrand(16) who demonstrated that neither breast nor bottle feeding favored development of oral candidosis. In the present study, even tube fed infants developed oral thrush the cause for which is not clear.

Well recognized risk factors for systemic candidosis such as prolonged administration of TPN, intravenous fluid and ventilation(19) were not important in the development of oral candidosis in the present study. Oral candidosis is a relatively early manifestation as compared to systemic candidosis, in which these factors are operative for prolonged periods of time.

Oral candidosis is likely to be widely prevalent in the future mainly because of increase in number of susceptible hosts. More research is needed for better understanding of the factors that predispose to oral yeast infections. Fortunately, the vast majority of cases of oral candidosis are not life threatening and readily respond to appropriately administered antifungal agents. However systemic dissemination of oral candidosis is known to occur. All oral candidal infections should thus be treated vigorously and effectively(20).

REFERENCES

1. Hay KD. Candidosis of the oral cavity. Recognition and management. Drugs 1988, 36: 633-642.
2. Baley JE, Kliegman RM, Fanaroff AA. Disseminated fungal infections in very low birth weight infants. Clinical manifestations and etiology. Pediatrics 1984, 73: 144-152.
3. Holmstrup P, Axell T. Classification and clinical manifestations of oral yeast infections. Acta Odontol Scand 1990, 48: 57-59.
4. Jorgensen EB. Etiology, pathogenesis, therapy and prophylaxis of oral yeast infections. Acta Odontol Scand 1990,48: 57- 59.
5. Oksala E. Factors predisposing to oral yeast infections. Acta Odontol Scand 1990, 48: 71-74.
6. Russell C, Lay KM. Natural history of *Candida* species and yeasts in the oral cavity of infants. Arch Oral Biol 1973, 18: 957-962.
7. Kay KM, Russell C. *Candida* species and yeasts in the mouth of infants from a special care unit of a maternity hospital. Arch Dis Child 1977, 52: 794-796.
8. Kaul KK, Shah JP, Pohowalla JN. Oral moniliasis in the newborn and neonatal morbidity. Indian J Pediatr 1960, 27: 115- 124.
9. Sharma NL, Gupta SP, Philip E, Goel KM. Neonatal candidosis. Indian J Pediatr 1965, 32: 157-162.
10. Rogers KB. Candida infections in pediatrics. *In:* Symposium on Candida infections. Eds. Winner HJ, Hurler R. London, Churchill Livingstone, 1966, pp 179-194.
11. Kostiala I, Kostiala AAI, Kahanpaa A. Oral mycoses and their treatment. Acta Odontol Scand 1979, 37: 87-101.
12. Lehner T. Oral thrush or acute pseudomembranous candidosis. Oral Surg 1964, 18: 27-37.
13. Jennison RF. Thrush in infancy. Arch Dis Child 1977, 52: 747-749.
14. Anderson NA, Sage DN, Spaulding EH. Oral moniliasis in newborn infants. Am J Dis Child 1944, 67: 450-456.
15. Cremer G, Degroot WP. An epidemic of thrush in a premature nursery. Dermatologica 1967,135:107-114.
16. Shrand H. Thrush in the newborn. Br Med J 1961, 2: 1530-1533.
17. Stenderup A. Oral mycology. Acta Odontol Scand 1990, 48: 3-10.
18. Kaloyannides TM. Oral moniliasis in the newborn. J Canand Dent Assoc 1968, 34: 496-497.
19. Smith H, Congdon P. Neonatal systemic candidiasis. Arch Dis Child 1985, 60: 365- 369.
20. Dreizen S. Oral Candidiasis. Am J Med 1984, *77:* 28-33.

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